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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/913,918	12/08/1997	DARWIN J. PROCKOP	TJU-1857	7733

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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/913,918	PROCKOP ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69,70,97-108,112 and 113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69,70,97-108,112 and 113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/24/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 71 and 77 have been canceled, claims 69, 102-104 and 112 have been amended by the amendment filed June 20, 2003, which has been revised to comply with the amendment rules on November 6, 2003.

The examiner acknowledges the telephone interview on May 27, 2003, wherein the examiner provides suggestions to amend the claims similar to that as amended by applicants in the currently presently pending claims.

The examiner also notes that a species restriction is currently on the record with respect to the species obesity factor. However, all of the currently pending claims are now have been amended to cancel the obesity factor species and other remaining species. The only claimed subject matter in this as-filed specification is the concept of employing genetically modified stromal cells or mesenchymal stems cells expressing a cytotoxic protein, wherein the cells are housed in a diffusible container, in order to inhibit the growth of tumor cells in an animal. In view of the examiner's telephone interview, wherein the examiner inadvertently invites applicant amend the claimed subject matter to that of the presently pending claims, and in view of the fact that applicant has canceled the all of other claimed embodiments, which were subjected to all previously outstanding rejections, the species restriction has been withdrawn by the examiner.

Claims 69-70, 97-108, 112, 113 are pending.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 113 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In dependent claim 113, the recitation of "the protein" is unclear and ambiguous since it is not apparent as to which of the two proteins as recited in the base claim, the term "the protein" refers to. A change to "said protein" is suggested, since that changed "said protein" would distinguish the term from the "cytotoxic protein" said in the base claim.

In view of the newly submitted prior art, *e.g.,* Gerson, US 5,591,625, and in view of the fact that mesenchymal stem cells are the same as bone marrow stromal cells (see Prockop, Science, IDS, Bruder, US 5,942,225, column 4, lines 29-30, 60-65), the following new ground of rejection is applicable.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 69-70, 97-108, 112, and 113 are rejected under 35 USC 103(a) as being unpatentable over Gerson (US Pat No. 5,591,625) taken with any of Naughton *et al.* (US Pat No. 5,858,721), Caplan *et al.* (US Pat No. 5,197,985), Schinstin *et al.* (US Pat No. 5,843,431), Mardon (previous cited prior art), and as evidenced by applicant's admission of the prior art of record as indicated on page 6 bridging page 7, and page 27 of the specification.

Gerson teaches a method of employing genetically modified msenchymal stem cells, wherein the transduced stems cells (MSCs) are contained in a porous ceramic cube device, and wherein the cells are transduced by a retroviral vector expressing more than one proteins, which proteins include a cytotoxic protein (thymidine kinase) and a secretory antibiotic resistant protein. Column 9, lines 5-8, column 10, lines 6-9, column 11, lines 30-51, column 12, lines 14-47, column 14, first full par.

While Gerson does not teach explicitly the concept of employing a porous container that physically isolates the MSCs from immune cells from attacking and degrades the implanted MSCs, such is well known in the prior art of record. For example, at the time the invention was made, the prior art of record, as exemplified by Naughton *et al.*, Caplan, Schinstin *et al.,* and Mardon, does teach that it is routine and conventional to use a microcarrier, diffusion chamber, or microcapsule to enhance the delivery and subsequent release and differentiation of the implantable mesenchymal stem cells to the target site (see entire document of each of the cited reference). Furthermore, the specification teaches on page 3 bridging page 7 that immunological

isolation means include well known technologies and devices such as microencapsulation, diffusion chambers, etc.

It would have been obvious for one of ordinary skill in the art to have employed any known a microcarrier, diffusion chamber, or microcapsule for the purpose of housing the MSCs and isolating them from immune cells, thereby enhancing the delivery and subsequent release of the implantable MSCs as disclosed in Gerson to the target site. One of ordinary skill in the art would have been motivated to have employed a microcarrier, diffusion chamber, or microcapsule to enhance the delivery and subsequent release of the implantable bone marrow stromal cells to the target site because of the reasons set forth in the immediately preceding paragraph. Note that use of well known technologies and devices such as microencapsulation, diffusion chambers, etc., as taught by the combined cited references, would physically isolate the isolated genetically modified stromal cells from the immune response, as evidenced by applicant's admission of the prior art of record as indicated on page 6 bridging page 7 of the specification.

In addition, one of ordinary skill in the art would have been motivated to transfect or transduce the cells of Gerson by conventional methods with vectors containing any known promoter, secreted signal sequences, beneficial protein, and/or a coding sequence of a selectable marker, such as those disclosed in the cited references to determine and track the effect of these regulatory elements and the subsequent expression of a desired gene by the stromal cells once implanted in an animal model.

It would also have been obvious for one of ordinary skill in the art to have

employed any pore size in any of the containers available in the prior art of record as an obvious matter of design choice particularly since such modifications would be expected to lead to an equivalent enhancement in delivery, release, expression and differentiation of the cells at the target delivery site, particularly in view of the absence of factual evidence showing an unexpected property of the use of the claimed pore size relative to those outside the claimed diameter of the pores of the claimed containers.

Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Gilbert, Transplantation, Vol. 56, 2, pp. 423-427, 1993, is cited to provide evidence demonstrating that even in 1993, carriers composed of biodegradable polymer scaffolds have been used routinely and successfully to study the delivery and expression of a therapeutically useful product in rats, and such study along with other cited references do show that at the time the invention was made, provide evidences showing that it is very common to those skilled in the art to actively employ improved biodegradable and/or biocompatible carriers to enhance gene delivery and expression of therapeutic protein products in *in vivo,* especially for the purpose of utilizing the thymidine kinase protein in combination with a prodrug to combat tumor cells in a tumor bearing subject.

Thus, the claimed invention as a whole as *prima facie* obvious.

Applicant's response filed June 20, 2003, particularly pages 5 and 6, has been considered by the examiner, but is moot in view of the new grounds of the rejection.

No claims are allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on June 20, 2003 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0184**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER